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Design and Measurement Considerations for Exercise Protocols in Human Air Pollution Inhalation Studies

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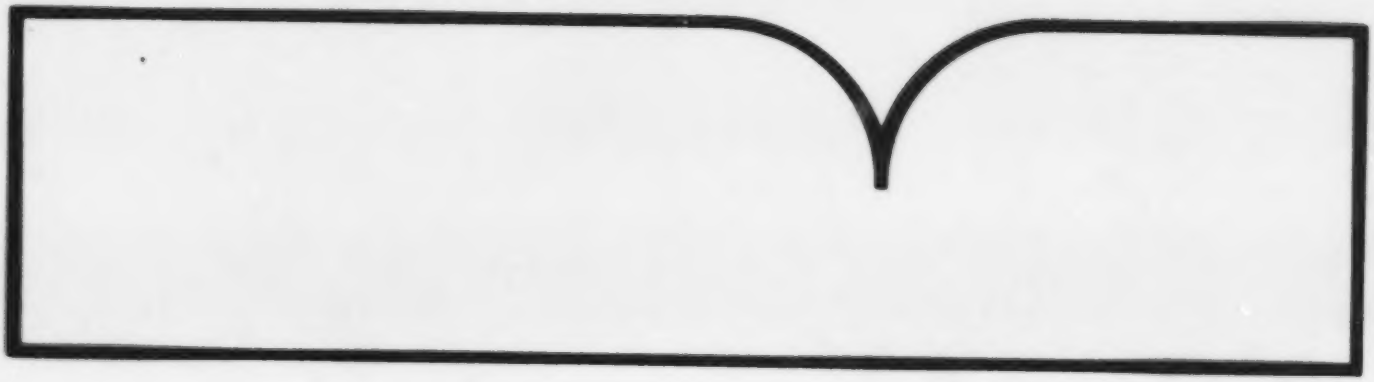

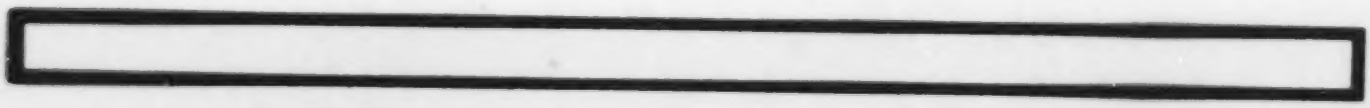

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16. ABSTRACT

The impact on pulmonary functions of exercising at different intensities during pollutant exposures was evaluated. It was apparent that there was considerable variation in exercise protocols. These variations occurred in the magnitude of the exercise load, the duration of the exercise period, and the timing of the exercise during exposure. It was also apparent that ventilation during rest and exercise was not always determined; in many instances ventilation was estimated based on other criteria, such as heart rate. The influence of ambient temperature conditions was frequently not considered. Determinations of pulmonary functions were also made at various time intervals following exercise or subsequent rest periods. All of these factors could result in some degree of misinterpretation of the consequences of pollutant exposure.

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Steven M. Horvath, M.D.[1]

Design and Measurement Considerations for Exercise Protocols in Human Air Pollution Inhalation Studies

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ABSTRACT: The impact on pulmonary functions of exercising at different intensities during pollutant exposures was evaluated. It was apparent that there was considerable variation in exercise protocols. These variations occurred in the magnitude of the exercise load, the duration of the exercise period, and the timing of the exercise during exposure. It was also apparent that ventilation during rest and exercise was not always determined; in many instances ventilation was estimated based on other criteria, such as heart rate. The influence of ambient temperature conditions was frequently not considered. Determinations of pulmonary functions were also made at various time intervals following exercise or subsequent rest periods. All of these factors could result in some degree of misinterpretation of the consequences of pollutant exposure.

KEY WORDS: exercise, air pollutants, pulmonary functions, air pollution, inhalation toxicology

The demonstration that decrements in pulmonary function are more striking in active individuals has been reinforced by a number of recent investigations. Previously, it had been noted in studies on quiescent subjects that minimal alterations in pulmonary function occurred in these resting subjects until the ambient ozone concentrations were relatively high. Only minimal decrements were observed at the lower concentrations, and marked decrements were observed only if the ambient ozone concentrations were quite in excess of levels recorded in even the most "polluted urban area." It should also be noted that there was a sex-related difference in the extent of forced expired volume in 1 s ($FEV_{1.0}$) decrement. Women appeared to be more responsive to oxidants than men.

Wayne et al [*1*] undoubtedly provided the stimulus to investigators to evaluate the responses of active individuals to oxidant exposure. Their studies were con-

[1]Director and professor, Institute of Environmental Stress, University of California, Santa Barbara, CA 93106.

ducted on athletes who occasionally competed in the Los Angeles area when pollutants (probably primarily ozone) were present at higher concentrations than was typical at the sites of their usual competitive meets. The performances of these athletes were reduced when competitions occurred in the Los Angeles basin.

Controlled studies in which exercise was introduced as a part of the experimental design were initiated by Bates and Hazucha [*2*]. It was clear from their data that greater decrements in usually determined pulmonary functions occurred when measurements were made in subjects who had been required to exercise during ozone exposure. Silverman et al [*3*] further demonstrated the importance of activity during ozone exposure in a series of studies. In these studies, subjects exercised intermittently during the controlled ambient exposures. In another study (ambient ozone concentrations of 0.75 ppm) it was noted that the capacity to perform maximal aerobic work was reduced by approximately 10% if the subjects had been exercising intermittently during the exposure. Horvath el al [*4*] exposed resting subjects to ozone (0.25, 0.50, and 0.75 ppm) for 2 h and reported that maximal aerobic work following the exposure was not affected. The difference between these two studies was apparently related to the magnitude of pulmonary function decrements induced during the prior exposure and to the level of activity and consequently the level of ventilation during the exposure.

The importance of activity, with its associated increase in inspired ventilation, to the alterations in pulmonary function is demonstrated in Fig. 1. It is apparent that, regardless of the time during an exposure to ozone that the exercise was undertaken, the decrements in pulmonary function were greater if measurements were determined immediately (within 3 to 5 min) following exercise and that a tendency toward recovery of functions occurred during the rest periods which followed the exercise period. The decrements in pulmonary functions became greater when exercise requiring larger ventilatory exchanges were undertaken. Studies were also conducted on subjects exercising continuously rather than intermittently during the exposure to ozone. Although this is not completely documented, it appears that continuous exercise and intermittent exercise induce equivalent effects on pulmonary functions if the products of ambient ozone concentration, minute ventilation, and duration of exercise are taken into account. The relative importance (contribution to pulmonary decrements) of these three factors appears to be related, respectively, to concentration, minute ventilation, and exposure time [*5*].

The literature [*6–8*] in which exercise was utilized to further delineate the magnitude of pulmonary decrements during pollutant exposure indicates that there were no consistencies in the procedures by which pollutants were given to the subject, in the level of exercise induced, the duration of the exercise during the exposure, the time at which exercise was induced during the exposure, and even the duration of the ozone exposure. Exposure to ambient pollutants varied from 5 to 360 min; the number of exercise periods varied from one to four during this time period; exercise duration varied from a single, short-term bout or a series of repetitive short exercise periods to continuous exercise during the exposure.

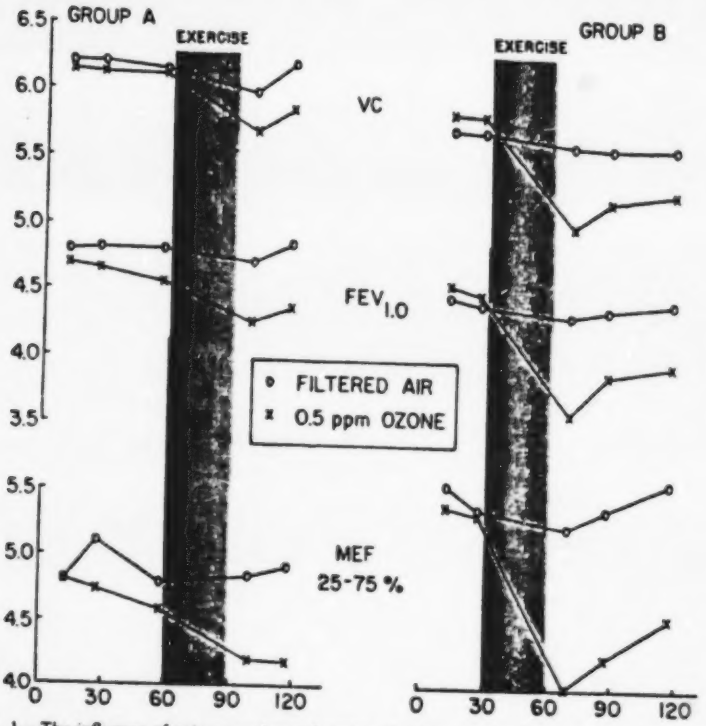

FIG. 1—*The influence of prior exercise and timing of pulmonary function measurements on the responses of vital capacity (VC), forced expired volume in 1 s ($FEV_{1.0}$), and maximal expiratory flow at 25 to 75% of vital capacity ($MEF_{25-75\%}$) during ozone exposure.*

The level of activity, that is, the pulmonary ventilation occurring during the exercise bouts, varied from twofold increases above resting ventilation (which was usually not determined) to minute ventilations of approximately 100 L.

Probably of greater importance in evaluating the pulmonary function decrements is that the time when pulmonary functions were measured after exercise varied from 3 to more than 20 min (sometimes hours), which raises the question of the significance of the measured values. In view of the prior observations that pulmonary functions tended to return to control levels when exercise was followed by a rest period, ventilation also tends to return rather rapidly to "resting levels" after the cessation of exercise.

Another, and probably the most confounding, factor relates to the failure of most investigators to actually measure the ventilation of their exercise loads. These investigators depend instead on utilizing such measures of exercise ventilation as (*a*) the work load (if a bicycle ergometer is used), (*b*) the heart rate during exercise, (*c*) different ventilations at fixed loads of work for individuals with high, intermediate, or low physical fitness because of marked individual

differences in capacities to perform exercise (Fig. 2), (*d*) sex differences (men versus women) in maximal aerobic capacities, either maximum aerobic capacity in litres (VO_2) or maximum VO_2 per kilogram per minute (women in general being some 20% lower than men), (*e*) the influences of the duration of exercise at certain work levels on the ventilation required to perform the work load—that is, a gradual increase in ventilation with time as fatigue develops, (*f*) differences in ventilations induced by exercise conducted on bicycle ergometers and on treadmills, (*g*) consideration of the effects of exposures conducted in hot environments on heart rate, minute ventilation, and the impact on performance due to the presence or lack of heat acclimatization [exposure to hot polluted environments (due to thermal effects) also affects expired ventilation (V_E) and breathing patterns, that is, increased breathing rate and decreased tidal volume (V_T) (if the body temperature is elevated)], (*h*) influence of the time of day (that is, circadian rhythm) on body temperatures and, thus, on both the heart rate and ventilation during exercise, (*i*) the chronic disease state of the subjects, and (*j*) the number of subjects utilized.

As exercise loads increase, there is also a shift of ventilating patterns from oral to oral–nasal; some individuals also are obligatory oral breathers. Additional problems relate to the mode of measuring ventilation. Consideration must be given to the alteration in breathing patterns and ventilatory volumes, which are modified if subjects breathe through mouthpieces or masks. Noninvasive techniques utilizing magnetometers or the respiratory-inductive plethysmograph could eliminate some of these problems.

In devising appropriate and valid experiments in which exercise is one variable, consideration must be given to a precise determination of what the experiment

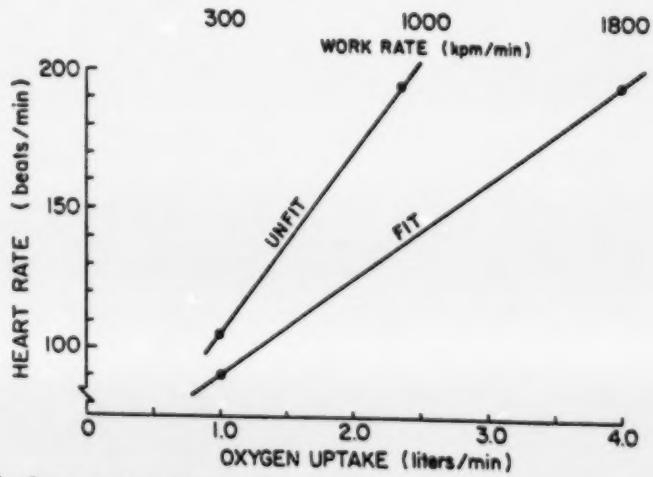

FIG. 2—*Oxygen uptake and heart rate responses of fit and unfit individuals to fixed work loads.*

is designed to elucidate. The major considerations that must be evaluated are the level of activity, the timing and duration of the activity during the exposure, the method(s) utilized to determine the exercise load, and, finally, the moment(s) at which the critical measurements defining the impact of the modified environment are to be made. Table 1 lists some of the many experimental conditions employed in studies involving pollutant exposure. There is no consistency in the exercise loads, the duration of exercise, the occurrence of exercise during the exposure, the duration of exposure, and the exact relationship of pulmonary function measurements to the exercise or rest period. Furthermore, as noted by Folinsbee in an accompanying paper [9], such variables as ambient environmental conditions, circadian periodicity, gender, age, "adaptation," and season have not been adequately considered.

All of these factors can induce minor or major constraints on the type, duration, and intensity of exercise utilized in various protocols. Additional factors that may influence results and interpretations are the level of physical fitness of the subjects, the impact of using trained and variable trained individuals, the number of subjects studied, the background history of the individuals volunteering to participate, a precise definition of the subjects' health or disease status (and capacity to perform exercise) (Fig. 3), the use of fixed exercise loads regardless of the physiological capacity of the individual, the use of relative work loads (that is, percentage of maximum aerobic capacity), failure to evaluate or appreciate the great variability in individual susceptibility to a particular pollutant or combination of pollutants, and other physiological or psychological conditions.

In addition to these factors, there are questions concerning technical details of measuring the ventilation during exercise. For example, some investigators have used a preliminary test to determine the work load to be utilized in the experiment proper. These preliminary studies offer no assurance that the estimates made at that time will continue to be applicable later. Naive subjects do not reproduce their conditions later. The only precise approach is to actually measure the metabolic parameters during each and every work load. However, it is appreciated that the usually available techniques utilizing mouthpieces and nose clips may interfere with pollutant exposure. Some questions have been raised as to the significance of the temporary alteration in breathing frequency, tidal volumes, and minute ventilations induced by these devices, but the value of actual measurement may override the questionable effects. Other devices are available, including masks, magnetometers, and a respiratory-inductive plethysmograph. These may provide valuable new methods for use in pollutant studies.

Another important variable relates to the duration of the measurement period. One-minute estimates of minute ventilation are unquestionably inadequate. A single, deep inspiration or the timing of the sample collections with respect to the stage of inspiration or expiration, or both, can appreciably alter the measured volume. Variations of up to 2 to 5 L have been observed in minute volumes measured repeatedly in steady-state work over a series of consecutive minutes. It should be appreciated that as exercise intensity increases, these differences in

TABLE 1—*Some examples of typical protocols utilized in pollutant studies. (All times are in minutes.)*[a]

SIMPLE PROTOCOLS

(a)	PF[b]	R 0 to 15	PF 15 to 20	E 20 to 35	PF 35 to 40	R 40 to 55	E 55 to 70	PF 70 to 75	R 75 to 90	E 90 to 105	PF 105 to 120 /PF			
(b)	PF[b]	E 0 to 15	PF 15 to 20	R 20 to 35	E 35 to 50	PF 50 to 55	R 55 to 70	E 70 to 85	PF 85 to 90	R 90 to 105	E 105 to 110	PF 110 to 115	R 115 to 120 /PF	
(c)	PF[b]	R 0 to 30	E 30 to 60	PF 60 to 65	R 65 to 90	E 90 to 105	PF 105 to 110	R 110 to 125 /PF						
(d)	PF[b]	E 0 to 30	PF 30 to 35	R 35 to 50	E 50 to 65	PF 65 to 70	R 70 to 85	E 85 to 100	PF 100 to 105	R 105 to 120 /PF				
(e)	PF[b]	R 0 to 60	PF 60 to 65	E 65 to 115	PF 115 to 120 /PF									
(f)	PF[b]	R 0 to 15	E 15 to 20	R 30 to 45	E 45 to 60	R 60 to 75	E 75 to 90	R 90 to 100 /PF						
(g)	PF[b]	E 0 to 10	PF 10 to 35											
(h)	PF[b]	E 0 to 30	PF 10 to 25	E 25 to 35	PF 35 to 50	E 50 to 60	PF 60 to 75 /F							
(i)	PF[b]	E 0 to 30	PF 30 to 45 /PF											
(j)	PF[b]	R 0 to 75	PF 75 to 85	R 85 to 120 /PF										
(k)	PF[b]	R 0 to 120	E 120 to 135	R 135 to 240 /PF										
(l)	PF[b]	R 0 to 90	E 90 to 105	PF 105 to 120	R 120 to 240 /PF									
(m)	PF[b]	R 0 to 120 /PF												
(n)	PF[b]	E 0 to 5	PF 5 to 25											
(o)	PF[b]	E 0 to 5	PF 5 to 25 /PF											

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								COMPLEX PROTOCOLS						
(a)	PF? 0 to 65	R	E 65 to 80	R 80 to 100	PF 100 to 125	R 125 to 185	E 185 to 200	R 200 to 220	PF 220 to 245	?				
(b)	PF? 0 to 80	R	E 80 to 95	R 95 to 100	PF 100 to 125	R 125 to 200	E 200 to 215	R 215 to 220	PF 220 to 245	?				
(c)	PF? 0 to 100	R	PF 100 to 125	R 125 to 220	PF 220 to 245	?								
(d)	PF? E 0 to 30	PF 30 to 45	?											
(e)	PF? E 0 to 60	PF 60 to 75												
(f)	PF? E 0 to 30	E 30 to 60	PF 60 to 75	?										
(g)	PF? E 0 to 60	PF 60 to 75	?											
(h)	PF? E 0 to 60	PF 60 to 75												
(i)	PF? R 0 to 30	E 30 to 70	PF											
(j)	PF? R 0 to 10	E 10 to 40	E 40 to 100	PF										
(k)	PF? R 0 to 10	PF 10 to25	E 25 to 35	PF 35 to 40	E 40 to 50	PF 50 to 65								
(l)	PF? E 0 to 30	PF 30 to 45												
(m)	PF? E 0 to 10	PF 10 to 25	E 25 to 40	PF 40 to 55	E 55 to 65	PF 65 to 70								

* This listing represents only a small fraction of the various protocols utilized. Additional studies have been performed after the subject was removed from the pollutant environment. Slash (/) indicates onset and end of exposure; R = rest, E = exercise of variable intensity, PF = pulmonary function measurements made while at rest, and ? = other tests, usually questionnaires (however, in some studies, questionnaires were given more frequently); it also represents a physician's evaluation, although in most protocols, the physician evaluation was performed before and after exposure.

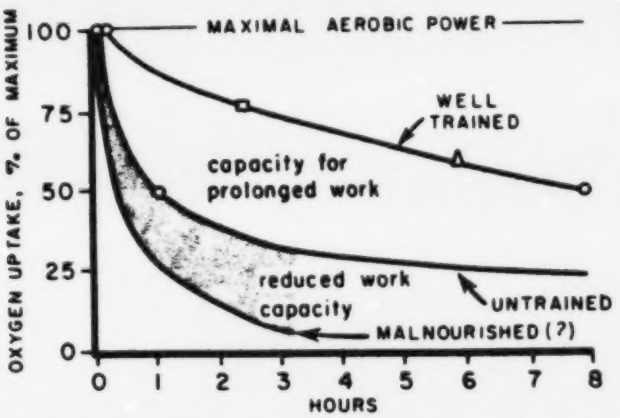

FIG. 3—*Duration of exercise in relation to the percentage of maximum aerobic capacity and relative state of physical fitness. These curves can be utilized to determine the duration of exercise at various work loads.*

minute volume measured over 1 min may exhibit even greater variability. If, in fact, it is useful (and in most instances it is) to determine more than minute ventilation, then 1-min collections become even less precise. If one accepts the premise that the percentage of maximal aerobic capacity ($\dot{V}O_2$) is a more precise procedure for evaluating individual subjects' (gender, physical training, and age) responses, then metabolic measurements need to be made, and these require more than 1 min to accomplish.

An additional difficulty becomes apparent in utilizing one measurement of minute ventilation if repeated exercise bouts or continuous exercise is utilized in the protocol. As subjects continue to exercise at higher intensities (that is, at >60% of $\dot{V}O_{2max}$), minute ventilation tends to increase with time. Consequently, unless ventilation is measured continuously, a single spot sample would provide spurious and unphysiological information as to the total ventilation over the exposure period. Precise data on ventilatory volumes is required if comparisons of different pollutant exposures are to be made employing the "effective dose concept."

The next question relates to the selection of the work load in a particular experimental design. Table 1 and Fig. 2 provide some insight into the difficulties of evaluating ventilation and work cost based on mean (average) information. As to the ventilatory exchange induced by the work load (metabolic cost), there is, in general, a linear relationship between heart rate and oxygen uptake. However, this idealized relationship hardly holds for any single individual. This implies that when a target minute heart rate (say 110, 150, or 170) is used as the basis for a statement concerning the magnitude of the work performed, it is subject to much qualification. Some investigators have performed studies using for a target heart rate an estimate based on the maximum heart rates attainable

by individuals of a given age. The typical predictive equation employed is as follows: maximum heart rate = 220 − age (years). This is hardly a precise method, and several modifications have been proposed with as little justification for their use.

There is some question as to the adequate utilization of the information in Table 2. Although this represents some acceptance in principle, it should be noted that, again, these data are a compilation from many sources, and individuals vary widely. The best estimate of the probability of making a correct estimate of ventilation from a given bicycle work load is ±15%. The estimates are also highly dependent on maintaining a fixed pedaling frequency. Trained bicyclists find it difficult and probably more energy-costly to pedal at low frequencies (50 to 60 rpm), preferring to cycle at 90 rpm or more. Since individuals have varying experiences with cycling, it is obvious that considerable estimate errors result. Regardless of whether bicycles or treadmills are used to exercise man, there is no easy way to estimate metabolic costs or even minute ventilation with acceptable precision except to *measure* directly. Even short-time measurements may not satisfy the requirements for preciseness.

Another approach that has been used but that, again, has little validity is the use of data which purport to show a linear relationship between ventilation volumes and oxygen uptake. Individual variability for this relationship is large. Furthermore, if one considers that the anaerobic threshold is not consistent among individuals, exercise loads near this threshold may produce further errors.

TABLE 2—*Some guestimates of minute ventilation based on work load.*[a]

Level of Work	Watts	Kilopond Metres, kpm	Oxygen Uptake, L/min	Ventilation, L/min
Light	25	150	0.65	13
Light	50	300	0.96	19
Light	75	450	1.25	25
Moderate	100	600	1.54	30
Moderate	125	750	1.83	35
Moderate	150	900	2.12	40
Heavy	175	1050	2.47	55
Heavy	200	1200	2.83	63
Very hard	225	1350	3.19	72
Very hard	250	1500	3.55	85
Severe	275	1650	3.91	93
Severe	300	1800	4.27	100+

[a]If exercise is conducted on a bicycle ergometer at 60 rpm (if rpms are higher, that is, 60+, values are different), it has been found that for the average fit individual (male), approximate values for oxygen uptake (L/min) and ventilation (L/min) can be assumed. However, wide individual variability occurs, and ventilation and oxygen uptake must be measured for each individual.

If exercise is conducted on a treadmill, no adequate relative standards for oxygen and minute ventilation can be assumed. In such activity there is an absolute need to measure both ventilation and oxygen uptake. Individual variability is great. In either exercise mode, the state of physical fitness, age, ambient temperature, level of training, and so on modify the estimated values. Other physiological factors may also result in altered predicted values. The only precise method of obtaining these data is to actually measure the ventilation and the oxygen uptake.

Little has been said about the influence of the intensity of the exercise bout, whether it is continuous or intermittent (single or multiple periods interspersed with, followed by, or preceded by rest periods), on the recovery ventilations and their impact on pulmonary functions measured in this recovery period. Clearly some pulmonary functional measures are influenced by the depth and rate of breathing at the time of measurement.

It is clear that minute ventilation during exposure is an important factor in determining the magnitude of change in selected physiological measures. Again, it is imperative to remember that, regardless of the intensity or pattern of the exercise and rest bouts, the most valuable information will be developed if the total lung volume exchange is known. It is also important, especially at the higher ventilations, to consider the role of oral–nasal contributions to inspired and expired ventilatory volumes. If exercise is conducted in that transitional zone "crossover" toward more oral ventilation, it should be recalled that this zone, though generally approximately 34 to 36 L/min (a number of studies have been conducted with exercise in this zone), is variable, with some subjects "crossing" at 15 L/min and others at 50 L/min. The questions raised by investigations exercising subjects at these levels of ventilation may have serious implications, and are impossible to define at this time.

What is the best exercise protocol? As shown in Table 1, a multiple number of designs have been utilized, differing in timing, duration, and intensity. If adequate determinations of metabolic-respiratory parameters are made, then it appears that any protocol may be acceptable, provided that the investigators justify the protocol selected in terms of the question(s) posed by the research. This may prove more difficult than to simply follow one or several suggested protocols. However, this writer prefers the former to the latter option. We may miss or misuse important information by redundancy and lack of imagination.

Probably as important as which exercise program is utilized in any study is the timing of the physiological measurements which will delineate the effects of the exposure and provide the information to speculate and prove the mechanisms involved. Table 1 also presents the extraordinary variability in the timing of the measurements of pulmonary function. In actuality, this portion of experimental design is producing more confusion in interpretation than the exercise portion of the protocol. It is suggested that attention be paid not only to "exercise" but to those physiological measurements that determine the "impairment of performance." The impact of exercising for 15 min during a 2 to 4 h exposure may well be lost if the physiological response is evaluated at some finite time after the exercise period, when it is possible that either or both the preceding and following rest period may "cover up" the effects one wishes to evaluate.

It is evident that multiple factors are involved in designing a theoretically pure exercise protocol to be utilized in air pollutant exposures. The variables involved include individual variability, technical details, and physiological states. The recommended solution to provide the best protocol is adequate justification by investigators for the protocol(s) being employed.

Acknowledgments

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